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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/31/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,260	KAWASHIMA ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2002* .

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-17,21 and 25-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-17,21 and 25-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All ☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *26* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed July 24, 2002. Applicants arguments and amendments presented in the response of July 24, 2002 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-14, 17, 21, 26-41, 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal (U.S. Patent No. 6,087,095).

Rosenthal teaches a method for sequencing nucleic acids comprising the steps of providing at multiple locations, a plurality of nucleic acid molecules hybridized to a primer to form target nucleic acid/primer complexes; contacting the target nucleic acid/primer complexes with a DNA polymerase and labeled nucleotides to allow for extension of the primer if a complementary nucleotide or plurality of nucleotides is present at the appropriate position in the target nucleic acid; detecting whether the labeled nucleotide is incorporated into the extended primer in order to determine the sequence of the target nucleic acid (see, for example, columns 7-8). In particular, Rosenthal (see column 7, lines 27-41) states that "(i)n an alternative embodiment of the invention, steps (c) and (d) of the first aspect of the invention are repeated sequentially a plurality of times before removal or neutralization of the label. The number of times that steps (c) and (d) can be repeated depends on the sensitivity of the apparatus used to detect when a labeled nucleotide has been added onto the primer". The method detects incorporation of at least 4-16 labeled nucleotides, with more sensitive devices being capable of detecting additional labeled nucleotides (columns 7-8). The nucleotide may be labeled with a radioactive or fluorescent moiety and is detectable by absorption or emission methods (columns 6 and 11). Rosenthal teaches that the sequencing method may be performed using labeled and unlabeled nucleotides and using a combination of dATP, dGTP, dCTP and dTTP or dUTP (column 6 and 8). With respect to claim 4, Rosenthal teaches removing excess unincorporated nucleotides by washing (see e.g., column 7, line 59 and column 11, lines 1 and 2). With respect to claims 5 and 14, the reference teaches immobilizing the primer or target nucleic acid onto a

solid support (column 4, lines 23-65) and detecting the labeled nucleotide without moving the extended primer to a different location (see, for example, column 11). The support may be a glass plate or a sequencing chip and may be an array of 100x100 pins or attachment areas. The reference further teaches that the sequencing method provides the advantage of allowing several DNA clones to be processed in parallel (column 3, lines 58-59) and particularly teaches method which allow for the simultaneous sequencing of 10^4 clones. In the method of Rosenthal, the labeled nucleotides can be used singly and sequentially until a labeled nucleotide is added, whereupon the sequencing steps are repeated. Alternatively, in an automated procedure, all four labeled nucleotides are added sequentially and an apparatus is programmed to detect which nucleotides are added to the primer (column 7). With respect to claims 35 and 36, the claims do not distinguish between the first and third location and thereby the limitation of the presence of a third location does not distinguish the claimed method over that of Rosenthal in which a plurality of single-stranded nucleic acids are added at a plurality of locations.

Rosenthal teaches that the sequencing method may be performed using labeled and unlabeled nucleotides and using a combination of dATP, dGTP, dCTP and dTTP or dUTP (column 6 and 8). Rosenthal does not specifically teach using a ratio of labeled to unlabeled nucleotides such that less than 50% of labeled nucleotides will be incorporated. Additionally, Rosenthal teaches repeating the primer extension and detection steps, but does specifically teach repeating these steps 19 times. However, to determine the optimum conditions for performing a method step is well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the

general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Rosenthal teaches that the ratio of labeled to unlabeled nucleotides and the number of cycles can be modified depending on the type of label used and the detection device. It would have been well within the skill of the art at the time the invention was made to have modified the method of Rosenthal so as to have used alternate ratios of the labeled and unlabeled nucleotides and to have selected the optimum number of cycles of primer extension and nucleotide detection in order to provided effective means for sequencing the target nucleic acid. It is noted that the specification as originally filed does not address the criticality of using labeled nucleotides that are incorporated at a level of less than 50% or 20% and does not address the criticality of performing 19 cycles. Accordingly, when taken as a whole, the teachings of Rosenthal would have lead one of ordinary skill in the art to the invention as now claimed.

3. Claims 15, 29, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal in view of Fu (Nucleic Acids Research (Feb 1997) 25:677-679; reference 'AK').

The teachings of Rosenthal are presented above. In particular, Rosenthal teaches hybridizing an oligonucleotide to the target nucleic acid to prime the extension reaction. Rosenthal does not teach using double-stranded DNA having nicks to prime the extension reaction.

Fu teaches methods for sequencing target nucleic acids wherein the methods utilize a double-stranded nucleic acid that has been nicked to provide a 3' terminus which serves as a

primer during the sequencing reaction. Fu teaches that the use of nicked double-stranded DNA for sequencing avoids the need to prepare and isolate single-stranded DNA and the need to synthesize primers, and avoids problems that arise due to secondary structure formation in single-stranded DNA (see page 679).

In view of the teachings of Fu, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rosenthal so as to have utilized nicked DNA as the template for sequencing rather than using a primer hybridized to the target DNA in order to have provided a highly effective template for sequencing a target nucleic acid and to have provided a simpler, more rapid means for sequencing which did not require generating single-stranded DNA or oligonucleotide primers and which would avoid problems associated with secondary structure formation that occurs when sequencing ssDNA molecules.

4. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal in view of Rabani (WO 96/27025; reference 'AH'). This rejection is based on the interpretation that the claims are inclusive of methods in which a single nucleic acid molecule is present at each of the first and second locations.

The teachings of Rosenthal are presented above. In particular, Rosenthal teaches immobilizing a plurality of the same target nucleic acid at a particular location. Rosenthal does not teach immobilizing only one nucleic acid molecule at a location.

Rabani (pages 7-8) teaches methods for sequencing nucleic acids comprising the steps of providing at multiple locations, a single nucleic acid molecule having a 3' terminus that may

serve as a primer in a primer extension reaction; contacting the target nucleic acid molecule with a DNA polymerase and labeled nucleotides to allow for extension of the primer if a complementary nucleotide or plurality of nucleotides is present at the appropriate position in the target nucleic acid; and detecting whether the labeled nucleotide is incorporated into the extended primer to thereby determine the sequence of the target nucleic acid. Rabani (page 7) teaches that sequencing with "the distinct single-molecule regime rather than with populations of identical molecules provides substantial advantages of parallelism, facility of use and implementation (including automated implementation) and operability."

In view of the teachings of Rabani, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rosenthal so as to have utilized single nucleic acid molecules rather than a plurality of identical nucleic acid molecules for sequencing in order to have achieved the benefits set forth by Rabani of improved parallelism, implementation and operability.

5. Claims 25, 29, 31-34, 36, 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal in view of Rava (U.S. Patent No. 5,545,531)

The teachings of Rosenthal are presented above. Rosenthal does not teach sequencing methods using an array having 1,000,000 locations and does not teach sequencing methods in which the nucleic acids are attached to a gel.

Rava teaches method for sequencing nucleic acids (column 11) using a chip having at least about 1,000,000 distinct locations for the attachment of nucleic acids (column 2). For

example, an array of .25mm^2 would have 1,000,000 locations for the attachment of nucleic acids (column 9). Rava (column 9) also teaches that the substrate to which the probes are attached may be a gel.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rosenthal so as to have used the arrays disclosed by Rava, particularly the arrays comprising a gel and containing at least 1,000,000 distinct locations for attaching the nucleic acids disclosed in order to have provided a more rapid and effective method in which more than 1,000,000 nucleic acids could be sequenced simultaneously.

6. RESPONSE TO ARGUMENTS

In the response of Paper No. 25, Applicants traverse the above rejections on the grounds that Rosenthal does not teach a method in which at least 19 cycles of sequencing are performed without removing incorporated labels. It is further asserted that Rosenthal does not teach a method in which the labeled and unlabeled nucleotides are provided in a ratio chosen so that the labeled nucleotides are incorporated less than 50% of the time. It is stated that Rosenthal does not teach the methods recited in claims 16 and 21 as amended. Applicants further argue that Fu and Rabani do not "add what is missing in Rosenthal."

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. While Rosenthal does not specifically exemplify a method in which less than 50% of the labeled nucleotides are incorporated or the sequencing cycles are repeated

19 times, such modifications of the method of Rosenthal would have been obvious to one of ordinary skill in the art at the time the invention was made. Rosenthal teaches that the ratio of labeled to unlabeled nucleotides and the number of cycles of sequencing can be modified based on the type of label and detection device employed. At the time the invention was made, optimization of sequencing reactions were well within the skill of the ordinary artisan and the ordinary artisan would have had a reasonable expectation of effectively performing sequencing methods that included performing additional cycles of primer extension and detection and which utilized decreased relative concentrations of the labeled nucleotides. Additionally, Applicants have not shown any criticality or unexpected results associated with methods which use the claimed ratios of labeled to unlabeled nucleotides or which use 19 cycles of sequencing. Accordingly, n the absence of evidence to the contrary, the claimed invention would have been obvious to one of ordinary skill in the art.

7. Claims 15, 21, 29, 35-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

A. The specification does not provide basis for the amendments to claims 15 and 29 set forth in Paper No. 25. While the specification (page 46) as originally filed provides basis for the concept of a method of sequencing wherein a "double-stranded molecule having a nick" is provided in place of a single stranded nucleic acid molecule, the specification as originally filed

does not provide basis for the concepts of performing nick translation reactions using labeled nucleotides in nick translation less than 50% of the time and "detecting how many of said nucleotides have been used per translated nick."

B. The specification as originally filed does not provide support for the amendments to claim 21 as set forth in Paper No. 25. In particular, the specification does not provide support for the claimed method in which the first primer extension product is removed, a second primer is added, primer extension is carried out using only "label-free" nucleotides, primer extension is then performed using only a "nucleotide bearing a label", and incremental base incorporations into the second primer are measured.

C. The specification as originally filed does not provide basis for the recitation in newly added claims 35 and 36 of a method in which a nucleotide sequence is added to a single stranded nucleic acid and then a plurality of single stranded nucleic acid molecules hybridized to a primer are added at a location.

D. The specification as originally filed does not provide support for the recitations in amended claims 37 and 38 of a method in which a third location is provided containing nucleic acids identical to the first location and wherein the third location is then treated with a polymerase and nucleotides in a manner identical to the first location.

8. Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35 and 26 are indefinite and vague. Claims 1, 7, 8, 9 and 25, from which claims 35 and 36 depend, require a single-stranded nucleic acid hybridized to a primer. Yet, claims 35 and 36 include an additional step of adding a nucleotide sequence that hybridizes to the primers. It is unclear as to whether the nucleotide sequences recited in claims 35 and 36 is the same as or different from the single stranded nucleic acid molecule recited in claims 1, 7, 8, 9 and 25. If the single stranded nucleic acid molecule is considered to be distinct from the nucleotide sequence, it is unclear as to the relationship between the nucleotide sequence and the remainder of the claim.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

January 23, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER